Remarks

Specification- A separate abstract page is provided herewith, said page to be added after page 60 of the specification, that is, the page immediately following the claims. The abstract submitted herewith is identical to the abstract as filed in the PCT application and as it published as WO 03/105766.

Claims-

Claims 1-9, 21-38, and 48-50 are presently under examination, claims 10-20 and 39-47 having been previously withdrawn.

Claims 1-9, 29-31, 33-38, and 48-50 are canceled herein without prejudice to their inclusion in a continuation application.

Claims 21, 25, and 32 have been amended herein. New claims 51, 52, and 53 have been added herein. Dependent claim 32 has been amended to depend from independent claim 21, instead of dependent claim 31, claim 31 having been canceled herein. No new subject matter has been introduced by amendment or the addition of new claims, which are fully supported by the specification and claims as filed.

Response to Assertion that Abstract as Provided When Entering National Stage is not Acceptable-

Applicants have provided the abstract as a separate page as requested and submit that the abstract is now in acceptable form.

Response to Rejection of Claims 21-24 and 48-50 under 35 U.S.C. § 112, first paragraph, enablement

Claims 21-24 and 48-50 stand rejected because it is the opinion of the Examiner that the specification, while being enabling for the treatment of some particular and specific neoplastic tumors or cancers, does not reasonably provide enablement for the treatment of any other disease or conditions characterized by inappropriate activity for reasons of record.

Examiner states the prior arguments by the Applicants are not persuasive.

Claims 48-50 have been canceled herein without prejudice to their inclusion in a continuation application. Therefore, the rejection as to these claims is moot. Applicants respectfully request that the rejection as to claims 48-50 be withdrawn.

At page 4 of the Office Action, Examiner asserts that the term "inappropriate Rsk activity" is not seen to be limited and includes any activity other than the ones recited by Applicants.

Examiner then asserts that some of the diseases described by the Applicants may not have an etiology that is related to Rsk activity alone. The Examiner further asserts that one of ordinary skill in the art will not expect to treat all of these diseases including ones not yet known, just by inhibiting Rsk activity.

The Examiner then states that specific flavones are demonstrated in the specification to inhibit Rsk. The Examiner asserts that the instant claims recite administration of a composition comprising an Rsk specific inhibitor, but that one of ordinary skill in the art will not extrapolate the activity of the flavones provided in the instant specification to any other compound or composition. It is the opinion of the examiner that undue experimentation is required to determine if a given compound or composition is an Rsk inhibitor before it can be used in the method.

The Examiner admits that the specification gives examples that use breast cancer and prostate cancer cells, but asserts that one of ordinary skill in the art will not extrapolate the results seen with these cell lines to the treatment of all other forms of cancer as recited in claim 49 and encompassed by claim 48.

The Examiner then asserts on page 5 that there is only enablement for "the specific flavones of formula I-III for the treatment of breast and prostate cancer.

Applicants traverse the rejection for the following reasons.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re*

Buchner, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

Although not necessarily agreeing with the reasoning of the Examiner, claim 21 has been amended herein to recite "cancer" instead of "a disease or condition", and to recite "excessive Rsk activity" instead of "inappropriate Rsk activity". These amendments are supported throughout the specification and claims as originally filed. For example, Rsk activity, etc., is defined and discussed on page 28, including, "excessive Rsk activity". Additionally, claims 51 and 52, which depend from claim 21 have been added and they recite the specific cancers, breast, prostate, and sarcoma (claim 51), as well as the specific flavones SL0101-1, -2, and -3 (claim 52). Each of these amendments is discussed below.

Under the present patent law, claims 21-24 as amended, as well as newly added claims 51 and 52, are enabled under 35 U.S.C. §112, first paragraph. The specification as filed amply supports these claims because the skilled artisan, armed with the methods disclosed in the specification, the compounds described therein, the methods of making the compounds, the assays as disclosed or known in the art, the cancers as disclosed or known in the art, would have been able to isolate and characterize, through routine experimentation, other compounds having the disclosed biological and biochemical activities as recited by the claims, and to practice the invention commensurate with the scope of the claims without undue experimentation.

Regarding the Examiner's assertion that the term "inappropriate Rsk activity" is not limited and includes any activity, the claims as amended recite that the "cancer" (amended from the term "disease or condition) is characterized by "excessive Rsk activity" instead of the term "inappropriate Rsk activity". Thus, one of ordinary skill in the art would know that the compounds would only be used to treat a cancer (not just any disease), and that the cancer was characterized by "excessive Rsk activity", not just any activity. Regarding the Examiner's comment that a disease may not have an etiology that is related to Rsk activity alone, Applicant's point out that the claims as amended now recite "cancer", which cancer must be characterized by "excessive Rsk activity". As disclosed in the application and discussed further below, regardless of the etiology of the cancer treated, use of an Rsk inhibitor selectively inhibited cancer cell proliferation and not that of normal counterpart cells.

Support for these amendments is found throughout the specification and claims as filed. For example, the description of "inappropriate Rsk activity" at page 28 of the specification (cited previously by the Examiner) states "The inappropriate Rsk activity may constitute overexpression of Rsk protein, excessive Rsk kinase activity or it may represent the expression of Rsk activity in tissues that normally do not express Rsk activity." (see page 28, lines 5-9). Applicants point out that the paragraph on page 28 begins with an introductory sentence which states that one embodiment of the present invention provides "a method for inhibiting Rsk kinase activity . . . as a means of treating an illness associated with inappropriate Rsk activity" (emphasis added). That introductory sentence is then followed by a description of inappropriate activity. Thus, the inappropriate activity refers to overexpression of Rsk (meaning greater than normal expression), excessive kinase activity of Rsk (which means that the activity of the Rsk is greater than normal, but one of ordinary skill in the art would understand that it could mean both an increase in the activity level of Rsk without an increase in the actual amount of Rsk, or that the increased activity could be due to more Rsk protein itself), or that there is expression of Rsk activity where there is normally no such activity. Further support for use of the term "excessive", and the like can be found in the first sentence of the Embodiments section of the application (page 9, lines 29-31), which states: "The present invention is directed to compositions comprising a Rsk specific inhibitor and methods of using such compositions for treating disease states related to Rsk hyperactivity." (emphasis added).

Applicants respectfully point out that the term "excessive Rsk activity", which replaces "inappropriate Rsk activity", is in the preamble of claim 21 as amended, which is further limited by the element "administering to a human or other mammal in need thereof" and by the element "an amount effective for specifically inhibiting Rsk activity", which refers to the amount of the compound to be administered. One of ordinary skill in the art would understand that the phrase "administering to a human or other mammal in need thereof" specifically limits the claim to those humans and other mammals in which cancer can be treated as claimed, not just any disease or condition. One of ordinary skill in the art would also appreciate that the element "an amount effective for specifically inhibiting Rsk activity" further limits and defines the claim by clearly indicating that a compound specifically inhibits Rsk activity.

Additionally, the present specification discloses that a variety of types of molecules can inhibit or reduce Rsk activity, Rsk levels, and in turn inhibit cancer cell proliferation of various kinds of cancer cells but not normal cells, including the use of compounds such as SL0101-1, SL0101-2, SL0101-3 (see figures) and siRNA (see page 36, lines 29-33). These data support the addition of new dependent claim 52. The invention further provides for other inhibitors, such as compounds comprising the general structures of the compounds of Formulas I and III, short hairpin RNA (page 19, lines 9-18), and antibodies directed against Rsk (see page 22).

Regarding Examiner's statement that "one of ordinary skill in the art will not expect to treat all of these diseases including ones not yet known, just by inhibiting Rsk activity", Applicants note that independent claim 21 as amended recites only "cancer", not all "diseases and conditions" and new dependent claim 51 recites a "cancer selected from the group consisting of breast cancer, prostate cancer, and sarcoma". The 3 types of cancer in claim 51 are all disclosed in the examples (and are more fully discussed below), and furthermore, represent a broad range of cancers, including carcinomas and sarcomas. Because claim 21 has been further amended to recite "excessive Rsk activity", instead of "inappropriate Rsk activity", Applicants submit that the specification fully enables the claim and that one of ordinary skill in the art will appreciate that the claims now recite treating a "cancer characterized by excessive Rsk activity".

One of skill in the art would also be able to treat a cancer by administering an Rsk inhibitor of the invention following the teachings set forth in the specification as filed and/or as known in the art based upon the disclosure provided in the specification without undue experimentation. That is, the crucial teachings of the invention, *inter alia*, discovery of a compound which inhibits Rsk, the role of increased Rsk activity in cancer, and the methods for making such compounds and treating cancer, are amply disclosed in the specification as filed (*see, e.g.*, Examples, and Figures). Therefore, the application merely omits that which is well-known to those skilled in the art and already available to the public, *i.e.*, specific diseases and the methods that a skilled artisan would used to treat such a disease. Moreover, such compounds are routinely screened in the art and administered and the practice of such methods is routine in the art and should not be considered an undue burden.

There is no requirement under the current law of enablement that each embodiment be reduced to practice. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991).

Amgen v. Chugai made clear that that enablement does not require working examples for each species encompassed by a claim under 35 U.S.C. §112, first paragraph. *Accord In re Robbins*, 166 USPQ 552 (CCPA 1970).

Additionally, the present application discloses that Rsk activity is required for proliferation of cancer cells. The present application further provides the first small molecule inhibitor of Rsk activity and shows that the inhibitor functions to halt the growth of the cancer cells, but not normal cells. Thus, the Rsk inhibitor induces the desired physiological response and can therefore be used to treat cancers characterized by over expression of Rsk or over expression of Rsk activity compared to that observed in the non-diseased tissue or expression of Rsk activity in tissues that normally do not express Rsk activity. The teachings embodied in this application were not part of the state of the art at the time of filing.

In fact, the present application demonstrates that the compounds described herein: 1) selectively inhibit cancer cell proliferation relative to normal cells and that the inhibition is reversible (see Figures 4, 7, 8); 2) that the compounds inhibited Rsk catalytic activity (See Figures 2, 3, 5); and 3) that the compounds inhibited Rsk2 kinase activity (see Figures 6, 10). The present application further discloses enzyme specificity of the compounds. Significantly, SL0101-1, -2, and -3 do not inhibit the evolutionarily related p70 S6 kinase and Mitogen and Stress-activated Protein Kinase (MSK). In addition, they do not inhibit the prototypical serine/threonine kinase Protein Kinase A or the tyrosine kinase Focal Adhesion Kinase (FAK) (Figure 3).

Examiner asserts that one of skill in the art would not be able to extrapolate the flavones used in the specification to "any" compounds. Applicants respectfully point out that amended claim 21 does not encompass any compounds, merely those with the general structure of III or with specific R groups, the SL0101- compounds, etc., and which have the ability to treat a cancer characterized by excessive Rsk activity by administering an amount of such compound effective for specifically inhibiting Rsk activity. Additionally, assays such as high throughput assays are provided for screening and testing such compounds, the specification provides methods for purifying and/or synthesizing compounds. For example, 1500 extracts were easily assayed when screening and discovering the *Forsteronia refracta* activity which inhibits Rsk activity (see page 10, lines 6-8, page 31, lines 3-28, and page 32, lines 5-8). Such assays are routine in the art and

do not require undue experimentation. Additionally, "effective amount" is discussed at page 5, lines 5-9, to mean an amount sufficient to produce a selected effect. For example, an effective amount of an Rsk inhibitor is "an amount of the inhibitor sufficient to suppress Rsk activity. Suppression of Rsk activity can be detected, for example, through the use of a serine/threonine kinase assay, such as the kinase assay described in Example 3". The specification as filed also describes methods for purifying such compounds, as well as synthesizing such compounds.

Examiner admits that the specification enables treating breast cancer and prostate cancer cells. Applicants note that the examiner failed to address "sarcoma", which was included in the previous response and was recited specifically in claim 50 (now canceled) in that response. However, the term sarcoma has been added to new dependent claim 51, which depends from claim 21. Applicants assert that the cancer sarcoma is enabled for the following reasons. For example, as detailed in Example 4, specific inhibition of Rsk inhibits proliferation of Ha-ras-transformed NIH/3T3 cells without influencing the proliferation rate of non-transformed NIH/3T3 cells (see page 39). Non-transformed NIH/3T3 cells are fibroblast-like cells. When fibroblasts are neoplastically transformed, they give rise to sarcomas. Ha-ras-transformed NIH/3T3 were originally obtained by neoplastically transforming non-transformed NIH 3T3 fibroblasts with the Harvey-ras oncogene. Thus, Ha-ras-transformed NIH/3T3 are sarcoma cells.

Applicants therefore respectfully submit, that in addition to breast and prostate cancer, the present application enables treatment of sarcoma cells with the compounds of the invention. Furthermore, because such a broad range of species of cancers is shown to be represented in the application as filed (i.e., carcinomas, sarcomas), Applicants assert that all cancers are enabled by the specification, particularly since the claims recite the cancer must be characterized by excessive Rsk activity.

For the reasons described above, Applicants respectfully submit that claims 21-24 as amended, and new dependent claims 51 and 52 are fully enabled and request that the rejection as to these claims be withdrawn.

Response to Rejection of Claims 21-32 under 35 U.S.C. § 112, second paragraph, indefiniteness

Claims 21-32 stand rejected as allegedly indefinite. The Examiner asserts that claims 21 and 25 are broad and not clear as to what applicants attend. The Examiner further asserts that the "specific activity" has to be recited in the claims.

Applicants are not sure as to the 'specific activity" to which the Examiner is referring, but will answer as related to the use of the phrase "inappropriate Rsk activity", which is recited in the preamble of claims 21 and 25, as well as the phrase "an amount effective for specifically inhibiting Rsk activity", as recited in original claim 21, and which has been added herein to claim 25.

Applicants traverse the rejection of the remaining claims for the following reasons.

Dependent claims 29-31 have been canceled herein, therefore, the rejection as to these claims is moot. Applicants request that the rejection as to these claims be withdrawn.

Claim 32 which had depended from newly canceled claim 31, has been amended herein to instead depend from claim 21.

First, Applicants point out that claim 21 as originally written specifically recites in the last line "an amount effective for specifically inhibiting Rsk activity...". Claim 25 has been amended herein to recite the same term. Second, as described more fully above, claim 21 has been amended herein to recite "excessive Rsk activity" instead of "inappropriate Rsk activity". Claim 25 has also been amended to now recite "excessive Rsk activity" instead of "inappropriate Rsk activity".

The reasoning described above for the use of these terms applies with equal force here.

One of ordinary skill in the art would understand that the description refers to "excessive Rsk activity", i.e., more Rsk in cancer cells than in normal cells, or to more Rsk activity in cancer cells than normal cells, and that the method refers to inhibiting Rsk activity, regardless of whether the activity is due to increased Rsk levels or increased Rsk kinase activity (described more fully above in the "Enablement" section). Therefore, Applicants submit that the activity as used in the claims is definite and is fully supported in the specification to allow adequate support of claims 21-27 and 32 as amended. Applicants further submit that new claims 51-52, which depend from claim 21, as well as new claim 53, which depends from claim 25, are supported by the specification as described above. For these reasons, Applicants request that the rejection as to claims 21-28, and 32 be withdrawn.

Response to Rejection of Claims 1 and 4-9 under 35 U.S.C. § 102(b), anticipation

Examiner asserts that Matthes et al. (Phytochemistry, 1980, 19, 2643-2650) anticipates claims 1 and 4-9.

Although not necessarily agreeing with the reasoning of the Examiner, Applicants have canceled claims 1 and 4-9 herein without prejudice to their inclusion in a continuation application. Therefore, the rejection as to these claims is now moot and Applicants respectfully request that the rejection as to these claims be withdrawn.

Response to Rejection of Claims 25-27 under 35 U.S.C. § 102(b), anticipation

Examiner asserts that Bjorbaek (WO 00/66721) anticipates claims 25-27 by teaching a method modulating body weight, fat content, leptin levels or oxygen consumption by altering or modulating Rsk activity using nucleic acid construct expressing Rsk2. The Examiner asserts that this teaching reads on treatment of disease/condition characterized by inappropriate Rsk activity as instantly claimed.

Applicants traverse the rejection of claims 25-27 for the following reasons. Applicants also respectfully submit that the following reasons also apply to new claim 53, which depends from claim 25.

It is well settled that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." See *In re Bond*, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990) and also MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." Id. (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Absence of any claim element from the reference "negates anticipation." *Kloster Speedsteel AB v. Crucible, Inc.*, 230 USPQ 81, 84 (Fed. Cir. 1986); *Rowe v. Dror*, 42 USPQ2d 1550, 1552 (Fed. Cir. 1992). Therefore, Bjorbaek must describe each and every element of amended claims 25-27 and new claim 53 in order to anticipate these claims under Section 102(b), and this reference does not.

Although not necessarily agreeing with the reasoning of the Examiner, as described more fully above, Applicants have amended claim 25 to specifically recite "cancer", instead of "a

disease or condition", "excessive Rsk activity" instead of "inappropriate Rsk activity", as well to recite the phrase "in an amount effective for specifically inhibiting Rsk activity". The addition of the latter phrase harmonizes the wording of claim 25 with claim 21. Therefore, claim 25 as amended reads:

"A method for treating a ~~disease or condition~~ cancer characterized by ~~inappropriate~~ excessive Rsk activity, said method comprising the step of administering to a patient in need thereof a composition comprising a Rsk specific inhibitor in an amount effective for specifically inhibiting Rsk activity".

Support for these amendments is also disclosed above, and the arguments provided above regarding these amendments and the changes in term language applies with equal force here.

Applicants assert that amended claim 25, as well as its dependent claims, is not anticipated by Bjorbaek, because Bjorbaek does not teach each and every element of any of these claims. That is, Bjorbaek does not disclose or contemplate "treating a cancer characterized by excessive Rsk activity" as claimed herein, nor does Bjorbaek teach or contemplate anything at all about excessive Rsk activity being involved in cell proliferation, much less that a cancer can be characterized by excessive Rsk activity or treated with an Rsk inhibitor (as claimed herein), and that using an Rsk inhibitor inhibits the proliferation of cancer cells, but not normal cells. In fact, Bjorbaek does not even contemplate cancer.

Furthermore, Bjorbaek does not teach or contemplate treating cancer with anti-sense oligonucleotides and interfering oligonucleotides as recited in dependent claim 26, nor does Bjorbaek teach or contemplate treating a cancer associated with excessive Rsk activity with an interfering oligonucleotide directed against an Rsk1, 2, 3, or 4 as recited in claim 27.

As pointed out in the prior response, nowhere does Bjorbaek use any construct, compound, or agent to modulate Rsk2 activity. Any reference thereto in Bjorbaek is speculation on the part of Bjorbaek, because Bjorbaek only disclosed a knockout mouse in which it measured body weight and similar parameters in the knockout relative to the wild type mouse. Bjorbaek does not address normal or cancer cell proliferation or disclose specific compounds which inhibit excessive Rsk activity associated with a disease such as cancer (which treats the cancer by inhibiting cell proliferation via inhibiting excessive Rsk activity) as disclosed and claimed in the

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present application. Moreover, Bjorbaek only mentions Rsk2, not any other Rsks, such as Rsk1, 3, or 4 as recited claimed in 27.

Applicants respectfully submit that claims 25, 26, 27 as amended, and new claim 53, are not anticipated by Bjorbaek and are now in condition for allowance. Applicants therefore request that the rejection be withdrawn.

Response to Rejection of Claims 2-3 and 33-38 under 35 U.S.C. § 103(a), obviousness

Claims 2-3 and 33-38 stand rejected as allegedly obvious over Matthes, Bjorbaek, Marks (U.S. 5,910,583), and Kuijpers (U.S. 5,733,523).

Although not necessarily agreeing with the reasoning of the Examiner, Applicants have canceled claims 2-3 and 33-38 without prejudice to their inclusion in a continuation application. Therefore, Applicants respectfully request that the rejection as to these claims be withdrawn.

Conclusion

If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (434) 243-6103.

Respectfully submitted,

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